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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,688	11/08/2001	Laurie H. Glimcher	HUI-037CN	3399

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,688	GLIMCHER ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 32-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 32-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The description of the drawings on pg 4, line 25 and 28, has been corrected.

The substitute specification with page numbers has been entered.

The computer readable format of the Sequence listing has been corrected by STIC by deleting invalid end of text files and has been entered.

Priority

The first line of the specification has been updated to reflect 09/181,716 has been abandoned.

Claims 2-31 have been canceled. Claim 52 has been added. Claims 1 and 32-52 are pending and under consideration in the instant office action.

Applicant's arguments filed 4-6-04 have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendment filed 4-6-04 is defective because the amendment to claim 1 is not based on the previous version of claim 1. A non-responsive letter should be sent out, but to expedite prosecution, an office action is being set forth. The amendment to claim 1 has not been entered because it is not based on the previous claim. It is noted that the preliminary amendment filed 11-8-01 did not amend claim 1, but the appendix of the claims in the preliminary amendment

shows claim 1 as a method claim. However, claim 1 as originally filed was a product claim. Therefore, in the previous office action, claim 1 was examined as it related to claim 1 as originally filed and the method claim in the appendix filed 11-8-01. Nor will claim 1 be examined as it relates to claim 1 in the response filed 4-6-04. Claim 1 is being examined only as it relates to the official version of claim 1 –originally filed claim 1.

Claim Objections

The term transgenic in claim 38 has been corrected.

In claim 49, steps 1-5 should be a)-e).

Claim Rejections - 35 USC § 101

Claims 1 and 32-51 remain and claim 52 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility for reasons of record.

Claims 1 and 32 are directed toward a transgenic mouse having a disruption of NFATp and NFAT4. Claims 1 and 32 do not require the mouse has a non wild-type phenotype.

Claim 45 are directed toward a method of identifying compounds that modulate immune cell activation via a pathway that does not involve NFATp or NFAT4 using a mouse with disruptions in the NFATp and NFAT4 genes characterized by increased Th2 cytokine production.

Claims 49 and 52 are directed toward a method of making a mouse that has increased Th2 cytokine production by breeding a mouse comprising a functionally disrupted NFATp gene with a mouse comprising a functionally disrupted NFAT4 gene. While the preamble of claim 49 states the mouse exhibits a phenotype characterized by increased Th2 cytokine production, the phrase does not bear patentable weight because it may not occur. Claims 49 and 52 do not require making a mouse with a non wild-type phenotype.

Claim 50 is directed toward a "mouse transgenic cell" with a disruption in the NFATp and NFAT4 genes.

The mouse of the invention has increased Th2 cytokine levels, slightly increased Th1 cytokine levels, increased IgE and IgG1, and slightly increased IgG2a and 2b levels (Example 3). The specification states that by inhibiting NFATp and NFAT4 activity using a compound, an increased Th2 activity may occur. Increased Th2 activity may be useful in treating disease states including encephalomyelitis (EAE), type I diabetes or rheumatoid arthritis (RA) in which an increased Th2 activity is desired (Section III, A).

Oukka (Immunity, 1998, Vol. 9, pg 295-304) taught mice having a disruption in NFAT4 had impaired development of CD4 and CD8 SP thymocytes and peripheral T cells and hyperactive peripheral T cells. Hodge (Immunity, 1996, Vol. 4, pg 397-405) taught mice having a disruption in NFATp had an enlarged spleen, hyperproliferation of B and T cells and an increase in Th2 activity. The art at the time of filing did not teach the NFAT4 or NFATp deficient mice were a model for disease or teach how to use the mice to screen

compounds. Since the time of filing, Rengarajan (Immunity, 2000, Vol.12, pg 293-300) and Ranger (Immunity, 1998, Vol. 9, pg 627-635) taught mice having a disruption in both NFATp and NFAT4. The art since the time of filing does not teach the mice are a model for disease or teach how to use the mice to screen compounds.

The mouse of the invention does not have utility. The mouse does not have a phenotype of a specific disease. No disease in humans was linked to a disruption in NFATp or NFAT4. While the mouse of the invention had swollen glands, swollen spleen, swollen eyelids, inflamed lungs, increased T cells, compromised FasL expression and defective apoptosis (claims 33-44), the specification did not teach how to use such a mouse as a model of disease.

The specification contemplated using the mouse to identify compounds that modulate NFATp or NFAT4 (Section III, line 3-6); however, the mouse does not express NFATp or NFAT4. Therefore, the compounds could not modulate NFATp or NFAT4.

The specification contemplated using the mouse to identify agents that modulate Th2 cell activity by means other than modulating NFATp or NFAT4 (pg 10, lines 31-34). Such a use is not substantial. Why would one of skill want a compound that did not modulate Th2 via NFATp or NFAT4? Is such a compound specific to a particular type of disease? What pathways that alter Th2 activity involve NFATp and NFAT4? What is the difference between compounds that alter Th2 activity via NFATp and NFAT4 and compounds that alter Th2 activity via other proteins? It would require one of skill further research to identify

pathways in which NFATp and NFAT4 modulated Th2 activity and to determine a use for a compound that modulated Th2 activity by acting on proteins other than NFATp or NFAT4. Identifying compounds that modulate Th2 activity by means other than modulating NFATp or NFAT4 is not a substantial or specific utility.

Applicants' description of the pending claims in the paragraph bridging pg 9-10 of the response filed 4-6-04 is inaccurate. Applicants have excluded product claims 1 and 32-44 that do not require identifying compounds or modulating immune cell activation "via a pathway that does not involve NFATp or NFAT4."

Applicants' argument that the claims do not require using wild-type animals is in error. Product claims 1 and 32 do not require a phenotype. Claim 49 does not clearly set forth in the body of the claim that the mouse produced from mating has increased Th2 activity. Claim 52 does not require the mouse made by mating has increased Th2 activity. Claim 49 is the only independent claim that requires mice having increased Th2 cytokine production.

Applicants' argument that the mice have utility because they can be used to identify agents that modulate Th2 activation via a pathway that does not involve NFATp or NFAT4 is not persuasive and has been addressed above (pg 10, 2nd ¶ of response).

Claim Rejections - 35 USC § 112

Claims 1, 32-51 and 52 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a

specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for reasons of record.

Upon overcoming the above rejection and describing a use for the mouse claimed, the specification does not enable making or using a transgenic having the disruptions as claimed with a wild-type phenotype (claims 1 and 32, 49, 50 and 52). The mice in Examples 1-3 do not have wild-type phenotypes. The specification does not teach how to use a wild-type mouse with a disruption in NFATp and NFAT4. Therefore, independent claims should be limited to mice having a phenotype described in the specification.

Applicants argue claim 1 is limited to a method. Applicants' argument is not persuasive because the amendment of claim 1 filed 4-6-04 has not been entered. Claim 1 was not amended in the preliminary amendment filed 11-8-01.

Claim 49 does not require the mouse having the disruption in both NFATp and NFAT4 has a phenotype that differs from wild-type, which is required for reasons cited above (the preamble is not given patentable weight in this case because the desired phenotype in transgenics may not occur).

Claims 45-48 are directed toward methods of screening compounds that regulate Th2 activity via a pathway that does not involve NFATp or NFAT4 using a mouse with a disruption in both the NFATp and NFAT4 genes. While one of skill could readily evaluate and compare the Th2 activity in the mice, the specification does not teach how the comparison leads to identifying compounds that regulate Th2 activity via a pathway that does not involve NFATp or NFAT4.

The compound may modulate a protein that binds NFATp or NFAT4 and be directly involved in "a pathway that involves NFATp or NFAT4." The determination of compounds that modulate Th2 via a "pathway that does not involve NFATp or NFAT4" as claimed is essential to the invention. Without such a disclosure, the specification does not provide adequate guidance for one of skill to determine compounds that modulate Th2 via a "pathway that does not involve NFATp or NFAT4" as claimed. It would require one of skill undue experimentation to determine compounds that modulate Th2 activity via a pathway that does not involve NFATp or NFAT4 as claimed.

Claims 32-51 remain and claim 52 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phenotype in claim 33 is found on pg 37, line 36.

The phenotype in claim 34 is found on pg 37, line 36.

The phenotype in claim 35 is found on pg 37, line 25-26.

The phenotype in claim 36 is found on pg 37, lines 30-33.

The phenotype in claims 37 and 38 is found on pg 38, lines 24-28.

The phenotype in claim 39 cannot be found and remains new matter. Applicants point to pg 38, line 30, through pg 39, line 28. It is readily apparent

that the citation states FasL was impaired and that FasL induction was compromised. Pg 39, line 11-13, mentions, "compromised FasL expression" but does not teach FasL expression is actually compromised. FasL expression may be compromised by a change in protein interactions or increased destruction of FasL; FasL expression may be "compromised" at a point later than expression – FasL expression may never be reduced. Claim 40 is included because it is dependent upon claim 39. Support for "defective apoptosis" in claim 40 is found on pg 39, line 13.

The phenotype in claim 41 is found on pg 39, line 31.

The phenotype in claim 42 is found on pg 40, line 5-7.

The phenotype in claim 43 of increased IL-4 dependent isotypes is found on pg 40, lines 13-15.

The phenotype in claim 44 is found on pg 40, line 13-15.

The phrase "identifying a test compound that modulates cell activation via a pathway that does not involve NFATp or NFAT4" in claim 4 is new matter. Pg 10, lines 33-34, suggests "identifying agents that modulate Th2 cell activity by means other than modulating NFATp or NFAT4 themselves." The breadth of compounds that modulate Th2 activity via any "pathway that does not involve NFATp or NFAT4" is broader in scope than compounds that modulate Th2 activity via "modulating NFATp or NFAT4 themselves" described in the specification. In addition, the breadth of "immune cell activation" is not the same scope as "Th2 activation" described in the specification.

The steps of claim 45 are described on pg 10, line 37, through pg 11, line 5.

Claims 47 and 48 remain new matter. The amino acid sequences of SEQ ID NO:1-3 were not described as being administered to mice. Pg 29, lines 15-38, and pg 21, lines 12-14 describe ways to inhibit NFAT using NFAT peptides; however, the mice claimed do not express NFAT. Therefore, it is not readily apparent that applicants contemplated administering the NFAT peptides of SEQ ID NO:1-3 to a mouse with a disruption in NFATp and NFAT4 to see whether it "modulates immune cell activation" as claimed.

The step of introducing an exogenous DNA molecule into a mouse ES cell such that the "wild-type" NFATp or NFAT4 gene is disrupted in claim 49 is new matter. Pg 9, lines 15, through pg 10, line 8, describe introducing an exogenous DNA molecule into a mouse ES cell such that the endogenous NFATp or NFAT4 gene is disrupted (pg 9, line 19, 22, 27, 29, 33 and 35). The term "wild-type" cannot be found in section I beginning on pg 9. It is unclear if the phrase is limited to "endogenous" genes – those naturally occurring in the ES cells or if applicants intend the phrase to mean any "wild-type" NFATp or NFAT4 gene found in any species that has been introduced into the ES cell.

The rejection regarding "murine" in claim 50 has been withdrawn in view of the amendment.

The rejection regarding ES cells and lymphoid cells in claim 51 has been withdrawn in view of pg 9, line 38, and pg 10, line 31.

Claim 51 remains rejected under new matter regarding fertilized egg cells. Pg 10, lines 6-8, contemplates germ cells, but does not contemplate fertilized eggs.

The phrase "a test compound that modulates immune cell activation via a pathway that does not involve NFATp or NFAT4" in claim 45 (preamble and step c) is new matter. Applicants point to pg 10, lines 32-34, which states lymphoid cells from NFATp/NFAT4 doubly deficient mice having increase Th2 activity can be used to identify agents that modulate Th2 activity by means other than modulating NFATp or NFAT4 themselves. The specification did not suggest testing for compounds that modulate any "immune cell activation." Nor does the specification define which pathways involve NFATp or NFAT4. Thus, the phrase is new matter.

Claims 1 and 32-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection regarding "exogenous" (1, 32, 49) has been withdrawn in view of the definition on pg 9, lines 7-10.

The rejection regarding "characterized" has been withdrawn in view of the definition provided. It is readily apparent that the term means the claim is limited to a mouse having that distinguishing feature.

The metes and bounds of what applicants consider "memory/activated phenotype" (claim 38) remains indefinite. Applicants argue pg 38, lines 23-28

defines the phrase. Applicants' argument is not persuasive. Pg 38, lines 23-28, teaches an increase in peripheral T cells with a memory/activated phenotype occurred as determined by low levels of mel-14 and CD45RB and elevated levels of CD44 and CD69. Pg 38, lines 23-28, does not define peripheral T cells with a memory/activated phenotype as being limited to low levels of mel-14 and CD45RB and elevated levels of CD44 and CD69. Nor does the specification teach how "low" is a low level of mel-14 or how "elevated" an "elevated level" of CD44 or CD69 is. Without such guidance, the metes and bounds of the memory/activated phenotype cannot be determined.

The rejection of claim 39 has been withdrawn in view of the amendment.

The metes and bounds of what applicants consider "IL-4 dependent immunoglobulin isotypes" (claim 43) remains unclear. Applicants point to pg 6, lines 10-13, which does not define IL-4 dependent immunoglobulin isotypes. Pg 6, lines 10-13, defines "Th2 cell activity" and does not mention any antibody isotypes that are dependent on IL-4.

The rejection regarding "calcineurin-interacting region of NFATp or NFAT4" (claim 46) has been withdrawn. It is readily apparent that the calcineurin-interacting region of NFATp or NFAT4 was known in the art and limited to Ser-Pro-Arg-Ile-Glu-Ile-Thr (SEQ ID NO:1) as described on pg 29, lines 22-31.

"[S]aid peptidic compound" in claim 48 remains indefinite because it lacks antecedent basis. Applicants argue the claim has been amended, but claim 48 has not been amended.

Claims 33-37, 39 and 41 are newly indefinite because claims 49 and 52 are not directed toward a transgenic mouse.

Claim 49 is newly indefinite because female mice are not "pseudopregnant" (steps 2 and 4). They are either pregnant or they are not. A "pseudopregnant" female would not produce an offspring as claimed. Only a pregnant female can produce offspring.

Claims 50 and 51 are indefinite because the phrase "mouse transgenic cell" is unclear. It is unclear if the phrase is limited to cells isolated from a transgenic mouse or if the phrase encompasses any mouse cell that has been genetically altered so that it has a disrupted NFATp gene and a disrupted NFAT4 gene.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER